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APPLICATION NUMBER: ***60/488,408***
FILING DATE: ***July 21, 2003***

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PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
MORDECHAI	DEUTSCH	MOSHAV OLESH, ISRAEL

☐ Additional Inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

AN EXPANDABLE CELL CHIP MATRIX

Direct all correspondence to: CORRESPONDENCE ADDRESS

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OR

☑ Firm or Individual Name	SCHOTTENSTEIN CELLOME RESEARCH CENTER				
Address	BAR ILAN UNIVERSITY				
Address					
City	RAMAT GAN	State		ZIP	52900
Country	ISRAEL	Telephone	+97235344675	Fax	+97235342019

ENCLOSED APPLICATION PARTS (check all that apply)

☑ Specification	Number of Pages: 6	☐ CD(s), Number	
☑ Drawing(s)	Number of Sheets: 3	☐ Other (specify)	
☐ Application Data Sheet. See 37 CFR 1.76			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

	FILING FEE AMOUNT ($)
☑ Applicant claims small entity status. See 37 CFR 1.27.	
☑ A check or money order is enclosed to cover the filing fees	$80.00
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☐ Payment by credit card. Form PTO-2038 is attached.	

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date 07/21/2003

TYPED or PRINTED NAME MORDECHAI DEUTSCH REGISTRATION NO. (if appropriate)

TELEPHONE 97235344675 Docket Number: 22

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60/488408 PTO 07/21/03

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13281 U.S. PTO
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FEE TRANSMITTAL for FY 2003

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☒ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 80

Complete If Known	
Application Number	
Filing Date	
First Named Inventor	MORDECHAI DEUTSH
Examiner Name	
Art Unit	
Attorney Docket No.	22

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☑ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☐ Deposit Account:

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The Director is authorized to: *(check all that apply)*

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FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	750	2001	375	Utility filing fee	
1002	330	2002	165	Design filing fee	
1003	520	2003	260	Plant filing fee	
1004	750	2004	375	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	80

SUBTOTAL (1) ($) 80

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent					=

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	84	2201	42	Independent claims in excess of 3
1203	280	2203	140	Multiple dependent claim, if not paid
1204	84	2204	42	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($)

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	410	2252	205	Extension for reply within second month	
1253	930	2253	465	Extension for reply within third month	
1254	1,450	2254	725	Extension for reply within fourth month	
1255	1,970	2255	985	Extension for reply within fifth month	
1401	320	2401	160	Notice of Appeal	
1402	320	2402	160	Filing a brief in support of an appeal	
1403	280	2403	140	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,300	2453	650	Petition to revive - unintentional	
1501	1,300	2501	650	Utility issue fee (or reissue)	
1502	470	2502	235	Design issue fee	
1503	630	2503	315	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	2809	375	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	2810	375	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	2801	375	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify)

*Reduced by Basic Filing Fee Paid SUBTOTAL (3) ($)

SUBMITTED BY				(Complete *if applicable*)
Name (Print/Type)	DR. ROBERT VASL	Registration No. (Attorney/Agent)		Telephone 972-2-5865515
Signature	RVasl			Date 07-21-2003

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PROVISIONAL PATENT APPLICATION

Inventor: MORDECHAI DEUTSCH

Title: AN EXPANDABLE CELL CHIP MATRIX

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to functional cellomics and, more particularly, to a method for the observation and manipulation of individual cells and their specific identified offsprings.

Combinatorial (bio)chemistry has evolved as an essential practical means permitting synthesis of many biologically-active and pharmaceutical structures, which must then be tested for their effects on animals and humans. The use of single, individual cell- based assays is an important tool in modern and advanced biomedical studies. Furthermore, cell functions are comprised of many interconnecting signaling and feedback pathways. Many times, a compound study based on isolated targets or cell preparations can not resolve this complexity. Thus, for a comprehensive understanding of a compound effect, testing of a single, whole living cell, is required. Such tests, in addition to their assistance in discovering and developing safer products, provide a useful tool in detecting biological and toxic effects, suggesting an alternative method for present toxicological tests resulted in reducing the number of animals used for testing.

In PCT patent application number WO 03/035824 to Deutsch filed 25 October 2001 there is described an example of an ordered matrix of wells configured for housing individual cells (cell chip) such as an interactive transparent individual cells biochip processor (ITICBP) that allows for the observation and manipulation of single cells in their own individual wells. A transparent cell chip enables performance of digital image analysis both on-line and off-line. The essence of the ITICBP methodology to Deutsch is the confinement of a single cell into

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a designed restricted space (micro-micro-liter-well) which allows multiple stages of manipulation and testing within the pico-liter-wells, among which static and kinetic measurements under various manipulations.

However this unique capability is a significant drawback when one is interested in the proliferation of one or more of the selected individual cells following multiple stages of manipulation and testing within the pico-liter-wells.

There is however a drawback associated with Deutsch's method. In Deutsch's method the cell chip offers a means for working and for observing individual cells. The cell chip can be used to select cells that would be used for cloning among the total population of cells that may be positioned in the wells of the cell chip. However when the cell for cloning has been selected it is difficult to clone as there is only enough room for an individual cell in each well and as a result the cell would have to be transferred to another position for cloning. This transferring is difficult and adds possible complication with these additional manipulations. The method of limiting dilution is widely used today for isolating individual cells for cloning and it is not a precise method due to the fact that the process as a whole is totally random, the father cell cannot be preidentified, and loss of cells occur during dilution and during suspension pouring into the microplate wells. Additionally there is no way to ensure the existence of only a single cell in a well if at all.

There is thus a widely recognized need for, and it would be highly advantageous to have, a method that separates individual cells by their localization via a proper well size - while later on supplying each of the tens of thousands of individual cells, enough "individual space" which will allow each of them, simultaneously, to proliferate while keeping their clone identity. In other words, there is a need to have only one identified cell in a given (known) well to start off with and on the other hand there is a need to have enough room for proliferation and all of this on the scale of many thousands of cells each in their own identifiable and accessible location on a cell chip. Furthermore following proliferation of the identified cells an accurately defined harvesting of specific clones made from the selected individual cells id required, while preserving at least a portion of the particular clone in a well defined location.

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BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawing. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawing:

FIG. 1 is a perspective top view of an unexpanded cell chip;

FIG. 2 is a perspective top view of an expanded cell chip following expansion; and

FIG. 3 is a perspective top view of an expanded cell chip following expansion and cell proliferation.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of an expandable interactive transparent individual cells biochip processor (cell chip) used for the cloning of pre investigated and selected individual cells.

The principles and operation of an expandable cell chip according to the present invention may be better understood with reference to the drawing and accompanying descriptions.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The

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invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Referring now to the drawings, Figure 1 illustrates a portion of a cell chip **10**. A cell chip **10** according to the prior art of Deutsch includes a glass or a rigid plastic cell chip unit **10**. A cell chip **10** according to the present invention is composed at least in part by an expandable element such as an elastic silicone rubber, or a plastic paraffin film. The size and number of the wells may vary as desired for example 50x50 wells of 20 μm diameter. The depth of the wells may be for example 10-20 μm.

After individual cells **22** have been loaded, identified and examined in individual wells of the unexpanded cell chip **10** for cloning, the cell chip **10** is expanded to a size that will enable enough room in each well to undergo separate clonal proliferation that will preserve the original identity and known address which enables the recovery of specific representative cells from each clone with the possibility of leaving at least some of the cells in their identifiable location.

Cells **22** illustrated in Figures 1 and 2 may be of any shape or size and are not necessarily attached to the bottom of the cell chip wells. The wells **20** may be of varying sizes to accommodate cells of any shape or size. Cells **22** in Figure 3 should preserve their own shape and size within each well **20** following clonal proliferation.

The expansion can be performed either manually or automatically by any one of numerous methods known to those skilled in the art in the plastic/elastic industry. A radial expansion as illustrated in Figure 1 is only an example of an expansion. A simpler expansion could be asymmetric, for example in one dimension. As a result of this asymmetric procedure, the physical direction of the cellular proliferation may be dictated due to the fact that the cellular well can be made in any required shape or form which will the cell proliferation will follow.

Figure 2 is an illustration of the cell chip **10** in the stretched form showing a single cell **22** in each expanded (macro) well **20**. The stretched wells now have room for cellular proliferation while maintaining its relative position. Figure 3 illustrates the cell chip **10** in the stretched form with cells that have undergone cellular proliferation with each well **20** containing a multiplicity of cells possessing the characteristics of the first cell in that particular well.

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In a further embodiment of the present invention the contents of the expanded or stretched cell chip (Figure 2 and 3) may be placed in another plate by selecting at least some of the cells and transferring them with the use of for example micro capillaries or by optical tweezers, or by placing the other plate on top of the expanded chip and then inverting the two such that some or all of the contents may be transferred to the other plate. In a further embodiment another plate may be used for additional step of expansion to further expand the well areas for further proliferation and so forth. This replication process enables the expansion of the wells to continue to sizes unobtainable by a single stretch of the first plate. The abovementioned inverting method enables simultaneous manipulation in a high throughput process and under an improved sterile environment. Following expansion, a gel layer may be placed on top of the proliferated cells such that the cells may grow into the gel and be further manipulated. A gel film may enable to observe the cells to provide necessary nutrients, markers and/or drugs to examine characteristic secretions of individual populations of cloned cells.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the present specification.

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WHAT IS CLAIMED:

1. An expandable cell chip essentially as described hereinabove or pictured in the figures.

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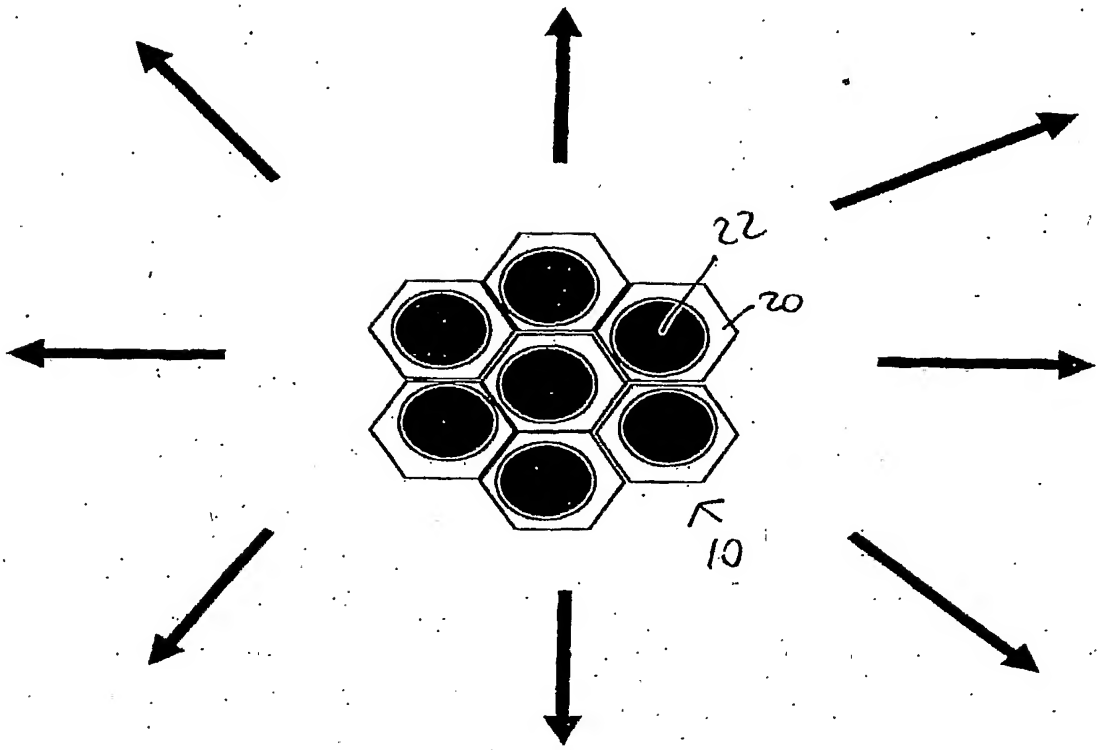

Figure 1

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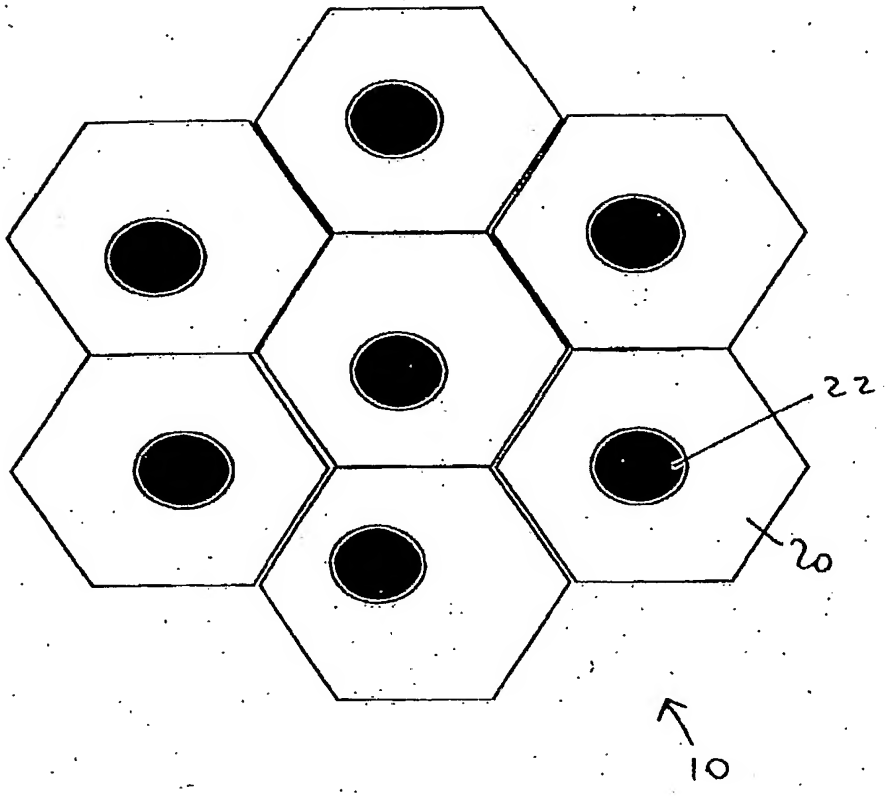

Figure 2

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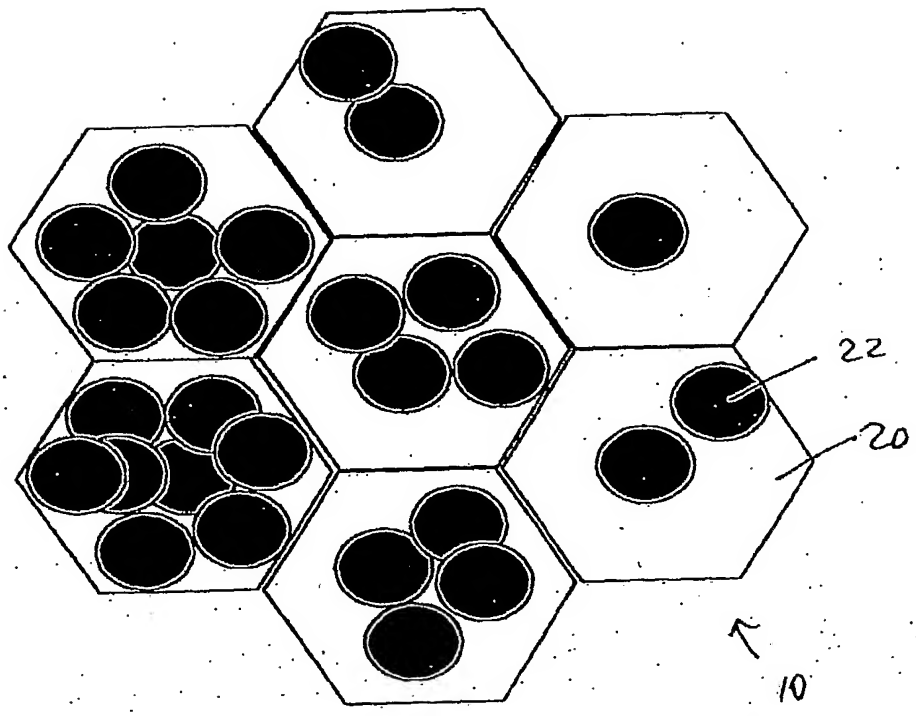

Figure 3

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